CLAIMS

What is claimed is:

1. A method for identifying candidate compounds for enhancing CREB pathway function comprising the steps of:

a) contacting host cells comprising an indicator gene operably linked to a CRE promoter with a test compound and with a suboptimal dose of a CREB function stimulating agent;

b) determining indicator activity in said host cells which have been contacted with said test compound and with said CREB function stimulating agent;

c) comparing the indicator activity determined in step c) with the indicator activity in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound;

d) selecting said test compound if:

i) the indicator activity determined in step b) is increased relative to the indicator activity in said control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound; and

ii) the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have been contacted with said test compound is not significantly different relative to the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have not been contacted with said test compound;

e) repeating steps a) to d) with a range of different concentrations of said test compound selected in step d); and

f) selecting said test compound if:

i) the indicator activity is increased in the range of concentrations for said test compound relative to the indicator activity in said control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound; and

ii) the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have been introduced said range of different concentrations of said test compound is not significantly different relative to the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have not been contacted with said test compound,

wherein said test compound is identified as a candidate compound for enhancing CREB pathway function.

2. The method of Claim 1 wherein said host cells are contacted with said test compound prior to contact with said CREB function stimulating agent.

3. The method of Claim 1 wherein said host cells are human neuroblastoma cells.

4. The method of Claim 1 wherein said indicator gene encodes luciferase.

5. The method of Claim 1 wherein said CREB function stimulating agent is forskolin.

6. The method of Claim 4 wherein steps a) to d) are repeated with a range of four different concentrations of said test compound selected in step d).

7. The method of Claim 1 further comprising the steps of:

g) contacting cells of neural origin with said candidate compound and with a suboptimal dose of a CREB function stimulating agent, wherein said cells of neural origin are different from the host cells of step a);

h) assessing endogenous CREB-dependent gene expression in said cells which have been contacted with said candidate compound and with said CREB function stimulating agent; and

i) comparing endogenous CREB-dependent gene expression assessed in step h) with endogenous CREB-dependent gene expression in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said candidate compound,

wherein a difference in CREB-dependent gene expression assessed in step h) compared to the CREB-dependent gene expression in control cells confirms that said compound is a candidate compound for enhancing CREB pathway function, thereby identifying said candidate compound as a confirmed candidate compound.

8. The method of Claim 7 wherein said cells of neural origin are contacted with said candidate compound prior to contact with said CREB function stimulating agent.

9. The method of Claim 7 wherein said cells of neural origin are neurons.

10. The method of Claim 9 wherein said neurons are primary hippocampal cells.

11. The method of Claim 7 wherein said CREB function stimulating agent is forskolin.

12. A method for assessing the effect on CREB-dependent gene expression of a candidate compound for enhancing CREB pathway function comprising the steps of:

a) contacting cells of neural origin with a candidate compound and with a suboptimal dose of a CREB function stimulating agent;

b) assessing endogenous CREB-dependent gene expression in the cells which have been contacted with said candidate compound and with said CREB function stimulating agent; and

c) comparing endogenous CREB-dependent gene expression assessed in step b) with endogenous CREB-dependent gene expression in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said candidate compound.

13. The method of Claim 12 wherein said cells of neural origin are contacted with said candidate compound prior to contact with said CREB function stimulating agent.

14. The method of Claim 12 wherein said cells of neural origin are neurons.

15. The method of Claim 14 wherein said neurons are primary hippocampal cells.

16. The method of Claim 12 wherein said CREB function stimulating agent is forskolin.

17. A method for assessing the effect on long term memory formation in an animal of a candidate compound for enhancing CREB pathway function comprising the steps of:

a) administering said candidate compound to be assessed to said animal;

b) training said animal administered said compound under conditions appropriate to produce long term memory formation in said animal;

c) assessing long term memory formation in said animal trained in step b); and

d) comparing long term memory formation assessed in step c) with long term memory formation produced in the control animal to which said candidate compound has not been administered.

18. The method of Claim 17 wherein said animal is a mammal.

19. A method for screening a compound for its ability to enhance CREB pathway function comprising the steps of:

a) contacting host cells comprising an indicator gene operably linked to a CRE promoter with a test compound, thereby producing a test sample;

b) contacting the test sample produced in step a) with a suboptimal dose of a CREB function stimulating agent;

c) determining indicator activity in said host cells which have been contacted with said test compound and with said CREB function stimulating agent;

d) comparing the indicator activity determined in step c) with the indicator activity in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound;

e) selecting said test compound if:

1) the indicator activity determined in step c) is increased relative to the indicator activity in said control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound; and

2) the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have been contacted with said test compound is not significantly different relative to the indicator activity in control cells which have not been contacted with said CREB function stimulating agent and which have not been contacted with said test compound;

f) repeating steps a) to e) with a range of different concentrations of said test compound selected in step e);

g) selecting said test compound if:

1) the indicator activity is increased in the range of different concentrations for said test compound relative to the indicator activity in said control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said test compound; and

2) the indicator activity in control cells to which have not been contacted with said CREB function stimulating agent and which have been introduced said range of different concentrations of said test compound is not significantly different relative to the indicator activity in control cells which have not been contacted with said CREB pathway function stimulating agent and which have not been contacted with said test compound, thereby selecting a candidate compound;

h) contacting cells of neural origin with said candidate compound selected in step g) and with a suboptimal dose of a CREB function stimulating agent;

i) assessing endogenous CREB-dependent gene expression in the cells which have been contacted with said candidate compound and with said CREB function stimulating agent;

j) comparing endogenous CREB-dependent gene expression assessed in step i) with endogenous CREB-dependent gene expression in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said candidate compound;

k) selecting said candidate compound if:

1) endogenous CREB-dependent gene expression assessed in step i) is increased relative to endogenous CREB-dependent gene expression in control cells which have been contacted with said CREB function stimulating agent and which have not been contacted with said candidate compound; and

2) endogenous CREB-dependent gene expression in control cells which have not been contacted with said CREB function stimulating agent and which have been contacted with said candidate compound is not significantly different relative to the CREB-dependent gene expression in control cells which have not been contacted with said CREB function stimulating agent and which have not been contacted with said candidate compound, thereby selecting a confirmed candidate compound;

l) administering said confirmed candidate compound selected in step k) to an animal;

m) training said animal administered said confirmed candidate compound under conditions appropriate to produce long term memory formation in said animal;

n) assessing long term memory formation in said animal trained in step m); and

o) comparing long term memory formation assessed in step n) with long term memory formation produced in the control animal to which said confirmed candidate compound has not been administered.

20. The method of Claim 19 wherein said host cells are human neuroblastoma cells and said cells of neural origin are neurons.

21. The method of Claim 20 wherein said neurons are primary hippocampal cells.

22. The method of Claim 19 wherein said indicator gene encodes luciferase.

23. The method of Claim 19 wherein said CREB function stimulating agent is forskolin.

24. The method of Claim 23 wherein steps a) to e) are repeated with a range of four different concentrations of said test compound selected in step e).

25. The method of Claim 19 wherein said animal is a mammal.